THE SERUM REACTION IN CANCER.*

REPORT FROM THE PATHOLOGICAL LABORATORY OF THE SKIN AND CANCER HOSPITAL OF NEW YORK CITY.

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IT is the object of this paper to record a series of observations upon the lytic action of the serum taken from cancer patients upon normal red blood-cells. Although the haemolytic properties of serum were discovered as long ago as 1875, by Landois, it is only within the last decade that any attempt has been made to apply the method of serum pathology to human disease! During recent years, however, the literature upon this subject has grown to very goodly dimensions. Of especial importance in the elucidation of the anæmias of certain diseases has been the discovery of "isohæmolysins" in certain human sera—in other words, the demonstration of the fact that such serra were capable of destroying the red corpuscles of other individuals. It has been shown by Ascoli, Eisenberg, and others, that the serum in cases of cancer, tuberculosis, syphilis, and certain other conditions frequently contain such isohæmolysins. This discovery, although of great theoretical interest, has not been capable of diagnostic application. In 1907 Weil showed that the serum of dogs afflicted with lymphosarcoma in an advanced stage was capable of destroying the corpuscles of normal dogs, but was markedly resisted by the corpuscles of other dogs afflicted with the same malady. This capacity for resistance by the red cells of other animals affected with the same disease appeared to offer a distinctive criterion, and was also made the basis of a study in human disease. An analysis of Weil's paper on the latter subject reveals the fact that in early malignant tumors the serum is hæmolytic in 46.5 per cent. of the cases, in 71 per cent. of which the corpuscles manifested a specific resistance;

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in late malignant tumors that it is hæmolytic in 71.5 per cent., and is resisted in 80 per cent. of these. In other diseases, the serum is hæmolytic in only 21.5 per cent., and such hæmolytic serum is less strongly resisted by the red blood-cells of the same disease producing such a hæmolytic serum, than is the case in cancer. If, however, easily identified conditions, such as pneumonia and advanced tuberculosis are excluded, the figure (21.5 per cent.) falls to 12.5 per cent. In normal individuals it is never hæmolytic. A comparison of these figures demonstrates that the factor of resistance on the part of the corpuscles adds materially to the accuracy and delicacy of the reaction. It appears to offer a fairly characteristic, though not pathognomonic feature, of cancerous disease.

The technic was as follows: About ten cubic centimetres of blood are withdrawn from the median vein of the patient whose blood is to be tested. One half to one cubic centimetre of this blood is immediately mixed with about fifteen cubic centimetres of a solution of 0.9 per cent. of sodium chloride to which 1.5 per cent. sodium citrate had been added. The remainder of the blood is then discharged into a test-tube, and allowed to clot. The corpuscles are now washed four times by centrifuging and resuspending in salt solution. After the last centrifugation they are suspended in sufficient normal salt solution to make up a ten per cent. emulsion. When the serum has separated from the portion of the blood, which is allowed to clot within the test-tube, it is pipetted, or poured off. Frequently it is mixed with some of the red blood-cells, which may be removed by centrifugation. The same procedure is then repeated upon the blood taken from a normal individual. The essentials for making the reaction, therefore, are: the clear serum from the cancer patient, and the clear serum from the normal individual; also a ten per cent. emulsion of red blood-cells from a cancer patient, and a ten per cent. emulsion of the red cells of a normal individual. From these ingredients are prepared the following six mixtures:

1.—0.5 c.c. of emulsion of normal cells; 1 c.c. of cancer serum.

2.—0.5 c.c. of emulsion of normal cells; 1 c.c. of serum from normal individual.

3.—0.5 c.c. of normal cells; 1 c.c. of normal salt solution.
4.—0.5 c.c. of emulsion of blood-cells from cancer patient; 1 c.c. of serum of normal individual.
5.—0.5 c.c. of emulsion blood-cells from cancer patient; 1 c.c. of serum from cancer patient.
6.—0.5 c.c. of emulsion of blood-cells from cancer patient; 1 c.c. of normal salt solution.

The series of test-tubes is now placed in the incubator for two hours, and then in an ice-chest over night. In every case the results were read within 24 hours from the time of taking the blood. Hæmolysis is at once evident by the "laked" or reddish color of the tubes in which it occurs as compared with the controls in salt solution. Those cases in which it occurred in tube 1, or in tubes 1 and 5, but not in the other tubes, have been recorded as positive.

The method as originally described by Weil involved the use of a number of cancer cases, and of a number of controls, the corpuscles of all of which were to be tested against the serum in question. It is evident that such a procedure, although practical with dogs, would add to the difficulties and complications of a clinical method. When available, it would enhance considerably the certainty of the reaction. The dilution of the serum with a fractional portion of the emulsion of red cells tends, of course, to intensify the hæmolytic power of the former, and may be reduced as low as one tenth, simply by using a twenty per cent. emulsion of red cells. In this way small amounts of blood could be made use of, and sufficient could be obtained from a number of normal individuals by merely pricking the ear.

These are variations of technic, which each investigator may make for himself.

Following out, however, the technic described by the author the details of the case are as follows:

EARLY CASES OR CASES OF CANCER, WITH SMALL AMOUNT OF MALIGNANT TISSUE PRESENT GIVING A POSITIVE REACTION.

CASE 1.—Lower lip; recurrent of epithelioma of lower lip about 1 inch in diameter, ulcerated; strength of reaction, +.

CASE 2.—Breast; recurrent carcinoma of breast; 2 operations; at the

first, one and a half years ago, breast was amputated. The second, one month ago, was for recurrence in supraclavicular glands; at present recurrence again in glands of neck, no ulceration, and although of long duration, there was no evidence that there was more than a small amount of cancer tissue present; strength of reaction, +.

CASE 3.—Breast; recurrent carcinoma in scar after removal of breast one year ago, not ulcerated; strength of reaction, +.

CASE 4.—Scalp; recurrent epithelioma in a gland of the neck following operation for removal of epithelioma of scalp, two years ago, affected gland was only the size of a walnut, and undoubtedly there was only a small amount of epithelioma tissue present; strength of reaction, +.

EARLY CASES, OR CASES OF CANCER, WITH SMALL AMOUNT OF MALIGNANT TISSUE PRESENT GIVING A NEGATIVE REACTION.

CASE 5.—Mouth; recurrent after operation for epithelioma of tongue.

CASE 6.—Cheek; Epithelioma of alveolar process 1 inch in diameter.

CASE 7.—Cheek; Epithelioma of inside of cheek and alveolar process of two months' duration.

LATE CASES OF CANCER, GIVING A POSITIVE REACTION.

CASE 8.—Tongue; large ulcerated epithelioma of tongue involving pillars of fauces, and tonsil; strength of reaction, + +.

CASE 9.—Lower lip; very large inoperable epithelioma of lower lip of long duration; strength of reaction, +.

CASE 10.—Inside cheek; large inoperable epithelioma of inside cheek, and alveolar process; strength of reaction, +.

CASE 11.—Cheek; large ulceration epithelioma of cheek 3 inches in diameter; strength of reaction, +.

CASE 12.—Breast; very large inoperable carcinoma of breast, ulcerated; strength of reaction, + +.

CASE 13.—Breast; recurrent carcinoma after amputation of breast in scar, ulcerated and advanced case; strength of reaction, +.

CASE 14.—Rectum; large carcinoma of rectum, ulcerated; strength of reaction, + + +.

LATE CASES OF CANCER, GIVING A NEGATIVE REACTION.

CASE 15.—Tongue; recurrent inoperable epithelioma of tongue.

CASE 16.—Cheek; large epithelioma presenting cauliflower growth 1 inch in diameter upon inside of cheek.

CASE 17.—Breast; inoperable cirrhotic carcinoma of breast.

CASE 18.—Breast; inoperable carcinoma of breast with axillary and clavicular glands.

CASE 19.—Breast; recurrent epithelioma from carcinoma of breast in glands above clavicle.

CASE 20.—Uterus; inoperable carcinoma of uterus.

CASE 21.—Uterus; inoperable carcinoma of uterus.

CASE 22.—Uterus; inoperable carcinoma of uterus.

CASE 23.—Uterus; large recurrent and inoperable epithelioma of cervix uteri involving vaginal wall, ulcerated.

CASE 24.—Œsophagus; inoperable carcinoma of œsophagus.

CASE 25.—Œsophagus; inoperable carcinoma of œsophagus.

EARLY CASES OF CANCER OF THE FACE OF RODENT ULCER TYPE, GIVING A POSITIVE REACTION,—*none*.

EARLY CASES OF CANCER OF THE FACE OF RODENT ULCER TYPE, GIVING A NEGATIVE REACTION.

CASE 26.—Face; small epithelioma of face; has received X-ray treatment.

CASE 27.—Nose; small epithelioma at side of nose undergoing cure by X-ray treatment.

CASE 28.—Ear; small epithelioma at back of ear, of rodent ulcer type.

CASE 29.—Upper lip; epithelioma of upper lip, of rodent ulcer type 1½ inches in diameter, ulcerated.

CASE 30.—Cheek; epithelioma of cheek 1 inch in diameter, of rodent ulcer type.

CASE 31.—Forehead; recurrent epithelioma of forehead, recurrent after X-ray treatment; is not ulcerated, and covers 1½ inches in diameter.

CASE 32.—Face; small epithelioma ¼ inch in diameter, now undergoing cure by X-ray treatment.

CASE 33.—Scalp; epithelioma of scalp 1 inch in diameter; also small gland in neck.

LATE CASES OF CANCER OF RODENT ULCER TYPE, GIVING A POSITIVE REACTION.

CASE 34.—Temple; epithelioma on temple 2 inches in diameter, slow growing of rodent ulcer type, ulcerated; strength of reaction, +.

LATE CASE OF CANCER OF RODENT ULCER TYPE, GIVING A NEGATIVE REACTION.

CASE 35.—Face; inoperable ulcerated epithelioma of rodent ulcer type involving antrum and orbit; a late case.

It has seemed wise to the author to place cancer of the face in a separate class by itself, because, both pathologically and clinically it is at least for such a long time in its history so entirely different from the usual forms of cancer.

To summarize. There were 20 late cases of malignant tumors (it is proper to include the late cases of cancer of skin in this list), of which eight yielded a positive reaction, or 40 per cent.

There were seven early cases of malignant tumors, of which four were positive, or 57 per cent. There were ten

cases of a relatively benign type of tumor (rodent ulcer), all of which, except one, were negative. This one, however, was an advanced case. Of the normal sera none showed any hæmolysis, but one case of chronic mastitis used as a control did show marked hæmolysis. As compared with normal sera, it is evident that the possession of isohæmolysins is a striking feature of the sera of patients with malignant disease.

This fact is certainly of great theoretical importance in explaining the cachexia and anæmia so characteristic of cancer. It is very striking, in this connection, that the tumors of a relatively benign type have absolutely failed to show the reaction, as they are marked clinically, by an absence of the anæmia so characteristic of the other forms of malignant disease. Moreover, the resistance of the red cells seems to be a fairly striking and constant feature, the significance of which is at once apparent, while its mechanism still remains, for further investigation.

The diagnostic value of the reaction may be considered from two standpoints. If negative, it is quite clear that the case cannot be regarded with certainty as free from cancer. If positive it is to be regarded with likelihood, as a case of malignant disease more especially if certain complicating infections giving the same reaction, such as advanced tuberculosis can be excluded. Although the writer has not examined other conditions of disease, it is evident from the results of others (Weil, Ascoli, etc.), that the typical reaction occurs in a very small proportion as compared with the cases of cancer; and in practically a negligible number of normal cases.

The statistics as obtained in the present series of cases compare quite closely with those published by Weil, the difference being such as would naturally be expected, within the margin of error, in a rather limited number of observations.

Averaging the percentages of positives obtained in the early and late cases, Weil obtained 59 per cent., and the writer 48.5 per cent. Finally, it is quite certain, as previously stated, that if the serum were tested upon a large variety of corpuscles, both from ascertained cases of cancer, and from

normal individuals, the percentage of positives could be very considerably increased.[1] It is to the obviation of such difficulties of technic that future investigation must be directed.

Tentatively, it might be suggested that suspected cases of cancer should have their serum tested, as herein described, against the normal corpuscle emulsion. If negative it would be advisable to make a second and more comprehensive test in the manner suggested.[2]

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[1] Such a course is justified, because of the practical unanimity among all observers as to the rarity of isohæmolysins in normal sera. It is to the facilitating of the technic by the use of small quantities of blood from a number of normal individuals, that future investigation must be directed. Such may demonstrate that we have in this test a material aid in diagnosis, but at the present writing with the evidence at hand, we cannot conclude that such is the case.

[2] The writer desires to express his thanks to Dr. Bainbridge and Dr. Torek, who have placed the material upon their service in the New York Skin and Cancer Hospital, at his disposal.

NOTE.—Since the above has been sent to press, the writer has read with interest the last publication by Dr. Crile, of his results of hæmolysis in cancer (Journal of American Medical Association, Dec. 12, 1908).

It hardly seems possible that the different technic, which Dr. Crile has made use of, can alone account for his results differing so widely from the observations here recorded. In this connection a reasonable doubt might be raised as to the accuracy of a method which permits the defibrinization of the blood, and the sedimentation of its cells twenty-four hours in the cold before they are utilized in the test.

Can the shaping of the whole blood with beads, and the subsequent exposure for twenty-four hours to the cold be less of a physical injury to the cells than the immediate centrifugation and utilization of the corpuscles?

Certainly, further investigation is needed to determine the real value of this reaction.